

Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Claims 1-6, 11-21, 23-26, 30-37, 42, 43, 64-67, and 73 have been canceled without prejudice. New claims 74-80 have been introduced. Descriptive support for claim 74 is provided in original claim 7. Descriptive support for claims 75-77 is provided in the description of the polynucleotide at Example 8. Descriptive support for claim 78 is provided at page 32, lines 7-9. Descriptive support for claims 79 and 80 is provided in Example 6. Descriptive support for the amendments to claim 7 is provided, *e.g.*, in Example 8 (*see* page 72, line 5) and page 34, lines 7 to page 35, line 12. Claims 38-41, 48-51, 55-60 are currently withdrawn but remain pending.

Applicants would like to request reconsideration of the restriction requirement, particularly as between the subject matter of sub-groups A and B (of Group II, as identified in Paper 4 imposing the restriction requirement). Sub-groups A and B represent the nucleic acid molecules encoding the tau and gamma subunits, respectively. As demonstrated in the present application, the tau subunit and gamma subunits (whether a -1 frameshift or a -2 frameshift product) are functionally and structurally similar. All of these subunits are naturally encoded by the same nucleic acid molecule that contains a frameshift site. (Clearly, as described at page 74, lines 11-17, recombinant nucleic acid molecules can be prepared that each encode only one of these subunits, but such nucleic acid molecules will share high identity.) As shown in Figures 4A-F, the tau and gamma subunits are identical between residues 1-453 (out of 529 for tau), and are distinct only with respect to their C-terminal regions. All three of these subunits contain the conserved ATP-binding region and Zinc-finger domain as identified in the alignment shown in Figure 5 and the corresponding description of the figure. For this reason, applicants respectfully request withdrawal of the restriction as between sub-groups A and B of Group II.

Applicants further request reconsideration of the restriction as between sub-groups A, B, and C (of Group II). The relationship between the subject matter of subgroups A and B is described above. Subgroup C relates to the *dnaE* nucleic acid encoding the alpha subunit. In replying to applicants response to the restriction requirement, the U.S. Patent and Trademark Office ("PTO") indicated reluctance to join this subject matter together despite PTO policy to the contrary (*see* 1192 O.G. 68 (November 19, 1996), cited in response to restriction requirement) and the public interest in resolving any interfering subject in as

timely a manner as possible. Applicants have identified potentially interfering subject matter in U.S. Patent No. 6,238,905 to McHenry et al. ("McHenry"), and apparently the above-noted PTO policy was *followed* during prosecution of the underlying McHenry application because no such restriction occurred in that case. Thus, applicants are merely requesting that PTO restriction policy be followed in a *consistent* manner, particularly given the possibility for an interference in this instance.

In addition to all of the above, applicants further request an explanation as to why claims 38-41 were not examined when these were identified in Paper 4 as belonging to Group II. There has been no basis provided for their withdrawal, and therefore such withdrawal is improper. Applicants would like the PTO to consider the fact that SEQ ID NOs: 6 and 8, recited in claim 38, are two oligomers that were utilized in the cloning of *Thermus thermophilus dnaX* (see paragraph beginning at page 58, line 18, as amended in the amendment filed November 21, 2003). Because claims 38-41 relate to subject matter currently under examination, the withdrawal of these claims appears to be in error.

For all these reasons, applicants respectfully request that the restriction requirement be withdrawn at least in part.

The objections to the specification are respectfully traversed in view of the above amendments to the drawings and the specification. The objections should therefore be withdrawn.

The objections to the claims are respectfully traversed in view of the above amendments and the following remarks, and should therefore be withdrawn.

The rejection of claims 8-10 under 35 U.S.C. § 112 (second paragraph) for indefiniteness is respectfully traversed in view of the above amendments and the following comment. With respect to the rejection of claim 10, applicants submit that the above amendment to the drawing makes clear that SEQ ID NO: 1 is properly recited therein.

The rejection of claims 7-10, 11, 12, 22, 23, 28, 29, 30, 34, 44, 45, 52, 61, and 68-72 under 35 U.S.C. § 112 (first paragraph) as lacking written description support is rendered moot with respect to canceled claims, and is otherwise respectfully traversed in view of the above amendments.

The PTO has basically taken the position that the specification fails to teach any claimed sequences other than the *dnaX* sequence of SEQ ID NO: 1 (encoding tau subunit

of SEQ ID NO: 2), and that these species are not adequately representative of the claimed genus. In addition, the PTO asserts that the specification fails to teach any particular structural/activity relationship. Applicants disagree.

As acknowledged by the PTO, the present application provides a nucleotide sequence and protein sequence for *Thermus thermophilus dnaX* (i.e., SEQ ID NOs: 1 and 3 for the nucleotide sequence, and SEQ ID NO: 2 for the amino acid sequence). Contrary to the above-noted assertion, the present application does identify a structural/activity relationship for tau subunits encoded by *dnaX*. In particular, Figures 4A-F and 5 identify structural features shared by many diverse prokaryotic tau subunits. Hence, there are certain structural features that would be expected by one of ordinary skill in the art to be conserved among the presently claimed genera of claims 7 and 44 given that even members outside the scope of the claimed genus (such as the *E. coli dnaX*) possess these conserved structural features. In particular, as shown in Figure 5 and recited at page 72, lines 5-6, the consensus GXXGXGKT motif for nucleotide binding is conserved in all these protein products. This conserved structure is related to ATP-binding, and the encoded tau subunit has ATP-binding activity. Other structural features of the polynucleotide and encoded tau subunit are described in Example 8 on pages 71-75. Another generally conserved structural feature of tau subunits is a four-cysteine residue zinc-finger domain (see Figure 5). The disclosed *Thermus thermophilus* polynucleotide also contains a hepta-A frameshifting site whose sequence comports with known frameshift heptamers, and two Shine-Dalgarno sequences located upstream of the frameshifting site. Because one or more of the conserved structures would be expected to likewise be conserved among polynucleotides from other thermophilic bacterium, including *Thermus* species such as *Thermus thermophilus*, it is clear that the present application identifies a structure/activity relationship for tau subunits and their encoding nucleic acids.

With respect to claim 7 and claims 8-10, 22, 28, and 29 dependent thereon, this claim presently recites that the claimed genus includes polynucleotides that “hybridize[] to the complement of SEQ ID NO: 3 under hybridization and wash conditions comprising 5X SSC at 65°C.” Given the structural and functional limitations presently recited in claim 7, applicants submit that the disclosure of the hybridization conditions and structure/activity relationship clearly indicates that applicants were in possession of the presently claimed genus at the time of filing.

With respect to claim 44 and claims 45, 52, 61, and 68-72 dependent thereon, applicants submit that the language recited in independent claim 44 is precisely the type of

claim language that was acknowledged in *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) as being acceptable under the written description requirement. In *Eli Lilly*, the Federal Circuit addressed the validity of several claims of U.S. Patent No. 4,652,525 to Rutter et al. (“Rutter”), specifically those claims that recited the limitations ‘vertebrate,’ ‘mammalian,’ or ‘human’ cDNA for insulin. Rutter disclosed the nucleotide and amino acid sequences of a rat cDNA encoding insulin, but merely described a general procedure for obtaining the human cDNA encoding insulin. *Id.* at 1567, 43 USPQ2d at 1405. The Federal Circuit found that the description of the rat cDNA did not provide adequate descriptive support for the narrow subgenus of ‘human’ cDNA (no species disclosed), the larger subgenus of ‘mammalian’ cDNA (only the one rat species disclosed), and the larger genus of ‘vertebrate’ cDNA (only the one rat species disclosed). *Id.* at 1567-68, 43 USPQ2d at 1405. The Federal Circuit did acknowledge, however, the district court’s statement that the specification provided adequate written descriptive support for the subgenus of ‘rat’ cDNA encoding insulin. *Id.* at 1566.

Thus, functional language should be acceptable when the genus as claimed is sufficiently limited in scope (i.e., from *Thermus thermophilus*) and the specification describes one or more species within that genus. Claim 41 recites the same type of functional claim language that was identified as acceptable in *Eli Lilly* given the description of a single species by its nucleotide sequence. Thus, it should be evident that claim 41 and claims dependent thereon find written descriptive support in the present application.

For all these reasons, the rejection of claims 7-10, 22, 28, 29, 44, 45, 52, 61, and 68-72 as lacking written descriptive support is improper and should be withdrawn.

The rejection of claims 7-10, 11, 12, 22, 23, 28, 29, 30, 34, 44, 45, 52, 61, and 68-72 under 35 U.S.C. § 112 (first paragraph) as lacking enablement is rendered moot with respect to canceled claims, and it otherwise traversed with respect to the remaining claims.

All that is needed is objective enablement of what is claimed. *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In particular, the present application provides the nucleotide sequence of a *Thermus thermophilus dnaX* (e.g., SEQ ID NOs: 1 and 3) and describes how one of ordinary skill can isolate other homologs of the disclosed sequence (*see* page 34, line 7 to page 35, line 12; Example 1), express the tau subunits encoded by such homologous *dnaX* sequences (*see* Examples 2-6), and test the encoded tau subunit for activity (*see* Examples 6 and 8). Thus, one of ordinary skill in the art

would have been fully able to make and use other polynucleotides within the scope of the presently claimed invention.

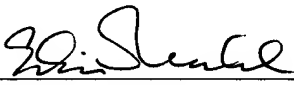
Therefore, the rejection of claims 7-10, 22, 28, 29, 44, 45, 52, 61, and 68-72 as lacking enablement is improper and should be withdrawn.

The rejection of claim 27 under 35 U.S.C. § 112 (first paragraph) as lacking enablement for vector pET*dnaX* is respectfully traversed. The PTO has taken the position that the vector is not completely disclosed, because the complete nucleotide sequence is not defined in the specification. Applicants submit that this is unnecessary for enablement of the invention of claim 27. In particular, the pET16b vector used by applicants remains commercially available from Novagen (see attached Exhibit 1), and the specification discloses both the nucleotide sequence of a *Thermus thermophilus dnaX* (e.g., SEQ ID NO: 3, Figure 4C) and how one of skill in the art can insert a *Thermus thermophilus dnaX* nucleotide sequence into the pET16b vector (see Example 3 and accompanying Figure 9). Use of the vector for expression of a His-tagged tau subunit is described in Example 4. For this reason, one of skill in the art is fully able to make and use a pET*dnaX* expression vector. The rejection of claim 27 for lack of enablement should therefore be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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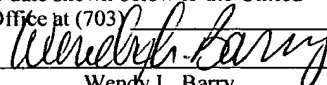
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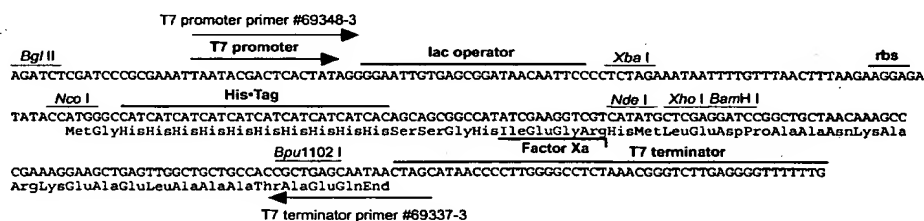
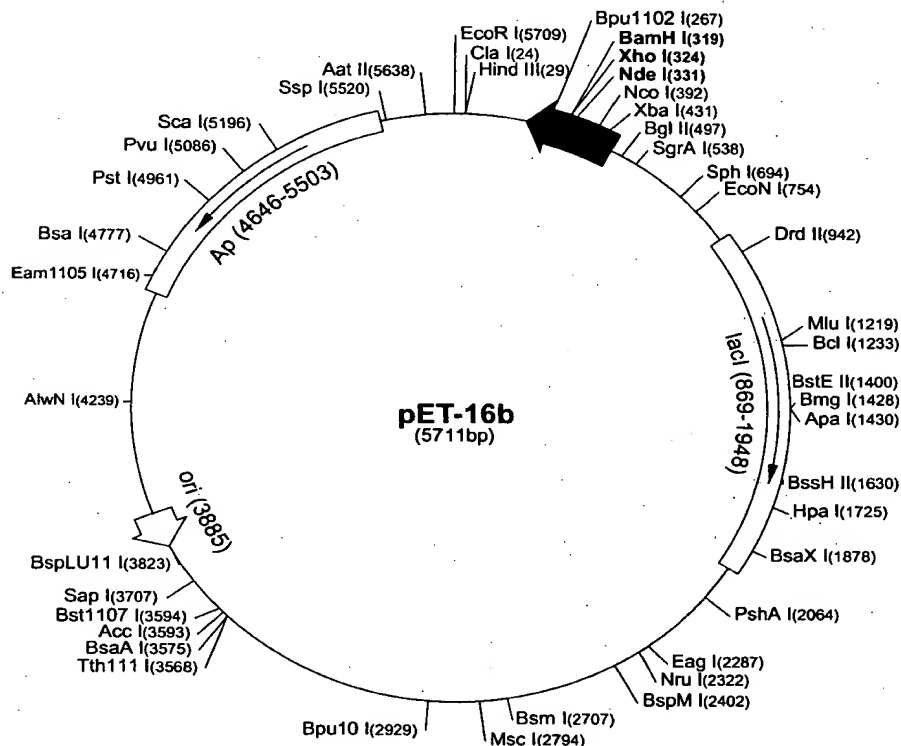
Amendments to the Drawings

Enclosed as an attachment to this amendment is corrected Figure 4B. The corrections to this page include changes to the nucleotide numbering to correct a typographical error. Number '1820' in the original should have been '1800', and all subsequent numbers below are likewise off by a count of 20 bases.

The pET-16b vector (Cat. No. 69662-3) carries an N-terminal His*Tag® sequence followed by a Factor Xa site and three cloning sites. Unique sites are shown on the circle map. Note that the sequence is numbered by the pBR322 convention, so the T7 expression region is reversed on the circular map. The cloning/expression region of the coding strand transcribed by T7 RNA polymerase is shown below.

pET-16b sequence landmarks

T7 promoter	466-482
T7 transcription start	465
His•Tag coding sequence	360-389
Multiple cloning sites (<i>Nde</i> I - <i>Bam</i> H I)	319-335
T7 terminator	213-259
<i>lacI</i> coding sequence	869-1948
pBR322 origin	3885
<i>bla</i> coding sequence	4646-5503



pET-16b cloning/expression region

pET-16b Restriction Sites

TB046 2/00

Enzyme	# Sites	Locations	Enzyme	# Sites	Locations	Enzyme	# Sites	Locations		
AatII	1	5638	BssHII	1	1630	PIIMI	3	801 2669 2718		
AccI	1	3593	Bst1107I	1	3594	PleI	7	480 768 855 1651 3717		
AccII	7	986 1714 2045 3332 3473	BstEII	1	1400			4202 4705		
		3775 5015	BstXI	3	1021 1150 1273	PshAI	1	2064		
Acil	89		BstYI	11		Psp5II	2	2787 2829		
AflIII	2	1219 3823	Cac8I	41		Psp1406I	5	881 2249 3148 4942 5315		
AluI	24		CjeI	26		PstI	1	4961		
AlwI	16		CjePI	28		PvuI	1	5086		
Alw21I	8	719 1203 2526 2817 3641	Clal	1	24	PvuII	3	1819 1912 3414		
		4141 5302 5387	CviJI	96		Rcal	4	617 4543 5551 5656		
Alw44I	4	1199 3637 4137 5383	CviRI	26		Rsal	4	165 1366 3629 5196		
AlwNI	1	4239	DdeI	11		SapI	1	3707		
Apal	1	1430	DpnI	29		Sau96I	22			
ApaBI	2	903 2400	DraI	3	4582 4601 5293	Sau3AI	37			
ApoI	2	1494 5709	DrdI	2	3516 3931	Scal	1	5196		
AvaI	2	324 2773	DrdII	1	942	ScrFI	24			
Avall	9	1771 2147 2235 2484 2787	DsaI	3	392 656 2795	SlaNI	24			
		2829 3108 4854 5076	EaeI	7	349 527 659 1893 2287	SicI	5	138 465 4088 4279 4957		
BamHI	1	319			2792 5104	SgrAI	1	538		
BanI	12		EagI	1	2287	SphI	1	694		
BanII	3	603 617 1430	Eam1105I	1	4716	Sspl	1	5520		
BbsI	5	1365 1704 2078 2941 5694	EarI	3	837 3707 5511	StyI	3	244 392 2717		
BbvI	28		Ecil	5	996 2743 3897 4043 4871	TaqI	14			
BccI	16		Eco47III	3	624 2125 3077	TaqII	8	1127 1345 2018 3725 5064		
Bce83I	7	208 2033 2203 3914 4212	Eco57I	2	4371 5383			5249 5402 5419		
		4453 5321	EcoNI	1	754	TfiI	7	1898 2200 2354 2652 2873		
BceII	5	738 1079 1706 2515 4325	EcoO109I	5	240 652 2787 2829 5692			3377 3798		
Bcgl	8	1511 1545 2045 2079 3400	EcoRI	1	5709	Thal	39			
		3434 5221 5255	EcoRII	10	129 942 1257 1797 1854	TseI	28			
BcII	1	1233			2406 2789 3849 3970 3983	Tsp45I	9	124 1400 2228 2495 3262		
Bfal	6	257 432 2837 4318 4571	EcoRV	2	187 1669			3475 3570 4972 5183		
		4906	FauI	18		Tsp509I	16			
BglI	3	2283 2517 4836	FokI	14		Tth111I	1	3568		
BglII	1	497	FspI	3	2706 2804 4938	Tth111III	7	1058 1751 3284 4413 4420		
Bmgt	1	1428	GdiII	6	349 527 659 1893 2287			4452 5708		
Bpml	6	1057 1546 2180 2734 3350			5104	UbaJI	24			
		4786	HaeI	8	947 2268 2340 2397 2794	Vspl	4	480 1904 1963 4888		
Bpu10I	1	2929			3838 3849 4301	XbaI	1	431		
Bpu1102I	1	267	HaeII	13		XcmI	3	1075 1591 1609		
BsaI	1	4777	HaeIII	29		XhoI	1	324		
BsaAI	1	3575	Hgal	15		XmnI	2	3381 5315		
BsaBI	3	496 502 3020	HgiEII	2	817 4409					
BsaHI	8	542 563 677 1176 1859	HhaI	44		Enzymes that do not cut pET-16b:				
		2554 5253 5635	Hin4I	5	16 1118 2489 4715 4789	AflII	Agel	AscI	AvrII	BaeI
BsaJI	11		HincII	2	1725 5257	BseRI	BsrGI	Bsu36I	DraIII	FseI
BsaWI	7	189 1538 2041 3012 4029	HindIII	1	29	KpnI	MunI	NheI	NotI	NsiI
		4176 5007	HinfI	14		NspV	PacI	PmeI	PmlI	RleAI
BsaXI	1	1878	HpaI	1	1725	RsrII	SacI	SacII	Sall	SexAI
Bsbl	2	3539 5259	HphI	17		SfiI	Sgfi	SmaI	SnaBI	SpeI
BscGI	13		MaeI	12		SrfI	Sse8387I	StuI	SunI	Swal
Bsgl	3	1070 1270 2983	MaeIII	18						
Bsil	3	3996 5380 5687	MbolI	15						
BsiEI	6	2004 2290 3739 4163 5086	MluI	1	1219					
		5235	MmeI	2	4038 4222					
BsII	22		MnlI	34						
BsmI	1	2707	MscI	1	2794					
BsmAI	7	916 1321 1447 1834 3464	MseI	24						
		4777 5553	MslI	10	1271 1559 1589 2379 2810					
BsmBI	2	1834 3464			3005 3396 4968 5127 5486					
BsmFI	4	680 2221 2446 3094	MspI	35						
BsoFI	52		MspAII	11						
Bsp24I	12		MwoI	44						
Bsp1286I	11		NarI	5	542 563 677 1859 2554					
BspEI	2	189 3012	NciI	14						
BspGI	3	2407 2484 3349	NcoI	1	392					
BspLU11I	1	3823	NdeI	1	331					
BspMI	1	2402	NgoAIV	4	529 2117 2277 2631					
BsrI	25		NlaIII	31						
BsrBI	3	452 3756 5557	NlaIV	28						
BsrDI	4	1266 1632 4777 4951	NruI	1	2322					
BsrFI	8	160 529 538 905 2117	NspI	4	694 3168 3460 3827					
		2277 2631 4796	Pfi1108I	2	2106 4734					